Cross-Linked Hyaluronate (Gel-One®)
National Drug Monograph
April 2013
VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary:[1,6]

- Gel-One® is a cross-linked hyaluronate (HA) product approved by the FDA for the treatment of pain associated with osteoarthritis (OA) of the knee in patients who have not adequately responded to non-pharmacologic therapy, NSAIDs, or simple analgesics (e.g. acetaminophen).

- It is the seventh HA or hylan product to become available for use in the United States.

- Gel-One® is administered as a single 3ml (30mg hyaluronan) intra-articular injection.

- Efficacy: Gel-One® was studied in a single clinical trial and was shown to be effective for up to 13 weeks in reducing Western Ontario and McMaster Universities Osteoarthritis Visual Analog Scale (WOMAC VAS) pain subscores. Other secondary endpoints including OMERACT-OARSI response, total WOMAC VAS Score, WOMAC VAS stiffness and physical function subscores were not statistically different between groups.

- No clinical trials are available comparing the efficacy of Gel-One® to other HA or hylan products, or for use in joints other than the knee. The safety and efficacy of repeat treatment courses with Gel-One® has not been studied and therefore is unknown.

- Safety: The most frequent adverse events reported with Gel-One® in the clinical trial were knee joint swelling (14.1%), knee joint effusion (11.2%), and knee/hip arthralgia (7.6%). No serious adverse events or deaths were reported. No post-marketing data for Gel-One® are available.

- No clinical trials using Gel-One® for off-label uses, such as intra-articular injection of the shoulder or hip, have been conducted. Only limited efficacy and safety data are available for use of other HA or hylan products in joints other than the knee (e.g., shoulder or hip).

- While other HA products are given as 3 to 5 injections per treatment course, Gel-One® was studied as a single-injection per course of therapy. Duration of efficacy was similar to several of the alternative HA products (e.g., 3 injection course of Supartz, Hyalgan, and Euflexxa) despite the shortened, single-injection course. However, a number of the HA products have a duration of effectiveness lasting up to 6 months per treatment course (e.g., Orthovisc-3 or 4 inj., Hyalgan-5 inj., Synvisc-3 inj). Synvisc-One is the other available viscosupplement that is administered as a single intra-articular injection and the treatment effect can last up to 6 months. Gel-One, Synvisc and Synvisc-One consist of chemically cross-linked HA resulting in increased viscoelasticity. Actual residence time of HA in the joint varies among products and should not be used to compare duration of efficacy of the HA products.

- The VA National Formulary does not currently include any HA or hylan products. Intra-articular corticosteroid injections are generally considered before intra-articular HA injections.

Introduction[1]

Gel-One® is a cross-linked hyaluronate product approved for the treatment of pain in osteoarthritis (OA) of the knee in patients who have not responded to non-pharmacological therapy, NSAIDs, or simple analgesics such as acetaminophen. There are currently six other agents available in the United States; Gel-One® is the seventh product to become available.

The purposes of this monograph are to (1) evaluate Gel-One®'s safety, tolerability, efficacy, cost, and other pertinent pharmaceutical issues for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its use in the VA.

Pharmacology/Pharmacokinetics[1,2,6]

Pharmacology:
Gel-One® is a sterile, viscoelastic hydrogel composed of cross-linked hyaluronate, which is a derivative of hyaluronan (sodium hyaluronate) that is extracted from chicken combs. Strands of hyaluronan are bound to each other via dimers of cinnamic acid, resulting in increased viscoelasticity.

Endogenous hyaluronic acid (HA) is released into the joint space after being produced by type B synoviocytes and fibroblasts. Hyaluronic acid has two functions in the joint: 1) during slow movement, the fluid acts as a joint lubricant and is more viscous, and 2) during rapid movement the fluid acts as a shock absorber and is more elastic. In OA, there is a smaller concentration of HA within the joint space. This causes pain due to decreased viscoelasticity in the joint, leading to altered joint mechanics, decreased lubrication, and damage to diseased cartilage within the joint.

The benefit of exogenous HA is not thought to be strictly mechanical. Exogenous HA products improve viscoelasticity within the joint and may also work through other mechanisms to benefit patients with OA. This includes inhibition of leukocyte chemotaxis, inhibition of lymphocyte proliferation, and inhibition of phagocytosis. Data also suggest there is inhibition of apoptosis, enzymatic cartilage degradation, prostaglandin E2, and other arachidonic activities. These physiologic changes can lead to increased endogenous HA production.

Pharmacokinetics:
A pharmacokinetic study was performed in rats after administration of a single subcutaneous injection of Gel-One®, using radioactive ^{14}C-labeled product. Max plasma concentrations (Cmax) occurred 7 days after injection for males and 9 days for females. Elimination was primarily renal. The time HA remains within the joint, or the residence time, is typically no more than hours to days; however, residence time should not be used to determine duration of analgesia for product comparison as the benefit of HA is not believed to be purely mechanical.

Table 1. Pharmacokinetics[2]

Half life (hrs) = 15 days in males and 21 days in females
Volume of distribution (L) = NA
Area under the curve (ug x hr/ml) = NA
Clearance (ml/min) = NA

FDA Approved Indication(s)[1]

Gel-One® is indicated for the treatment of pain associated with OA of the knee in patients who have not adequately responded to non-pharmacologic therapy, NSAIDs, or simple analgesics (e.g. acetaminophen).

Potential Off-label Uses[2,6]

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP-VPE and the Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

At this time, there are no studies examining the safety and efficacy of Gel-One® in joints other than the knee. Some case series and open-label experiences with a small number of patients discuss the use of other HA or hylan products in joints such as the hip, shoulder, or ankle. In general, use of HA for joints other than the knee cannot be routinely recommended due to the lack of available evidence. No data specific to Gel-One® for off-label uses are available and therefore off-label use is not recommended.

The safety and efficacy of repeat treatment courses with Gel-One® has not been studied and therefore is unknown.

Current VA National Formulary Alternatives[5,6]

The VA National Formulary does not currently include any HA or hylan products. Intra-articular corticosteroids may be considered as an alternative, and these agents are generally attempted prior to HA products. Non-formulary alternatives to Gel-One® include:

Table 2: Alternative Hyaluronate or Hyaluronan/Hylan Products

	Description	HA dose per Injection	Volume per injection	Injections per Course	Duration of Pain Relief
Gel-One®	Cross-linked hyaluronate	30mg	3ml	1	13 weeks
Supartz®	Sodium Hyaluronate	25mg	2.5ml	3 or 5	3 inj: 90 days 5 inj: 6 months
Hyalgan®	Sodium Hyaluronate	20mg	2ml	3 or 5	3 inj: 60 days 5 inj: 6 months
Euflexxa®	Sodium Hyaluronate	20mg	2ml	3	3 months
Orthovisc®	High molecular weight hyaluronan	30mg	2ml	3 or 4	6 months
Synvisc®	Hylan G-F 20 (Hylan A fluid 80% and Hylan B gel 20%) [Cross-linked polymers of hyaluronan]	16mg	2ml	3	6 months
Synvisc-One®	Hylan G-F 20 (Hylan A fluid 80% and Hylan B gel 20%) [Cross-linked polymers of hyaluronan]	48mg	6ml	1	6 months

Dosage and Administration[1,2,3]

Gel-One is available as a single 3 ml syringe (1% solution [10mg/ml], 30mg total hyaluronan) intended for intra-articular injection, and is expected to provide pain relief for 13 weeks. It is administered similarly to other HA products. Refer to the prescribing information for detailed directions on proper administration. Strict aseptic technique should be used. The manufacturer recommends no renal or hepatic dose adjustments are necessary.

Efficacy[1,4,5,6]

Existing evidence does not support that any HA or hylan product is more efficacious or safer than another. The efficacy and safety of Gel-One® was evaluated in a single clinical study as follows:

Efficacy Measures

- Reduction of Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) VAS pain scores
    - The WOMAC is an index used to assess patients with osteoarthritis of the knee or hip regarding pain, physical function, and stiffness. The pain subscore specifically assesses pain when walking, pain associated with stairs, nocturnal pain, resting pain, and weight bearing pain. A 100mm Visual Analog Scale is used to assess each of these areas.
    - The primary endpoint (WOMAD VAS pain score) was analyzed using spline modeling, utilizing all available WOMAC VAS pain score data through week 13. Longitudinal modeling assessed the primary endpoint at baseline and for weeks 6 through 13. The longitudinal model was used as the confirmatory model.
- OMERACT-OARSI (Outcome Measures in Research Society International) Response
    - Measures pain, physical functioning and patient global ratings in a single validated measure of patient response.
- Total WOMAC VAS score
- Physician Global Evaluation
- Subject Global Evaluation
- SF-36 physical component score (PCS), health status questionnaire
    - Assesses 8 subscales: physical functioning, limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, limitations due to emotional problems, and mental health. There are two summary component scores, 1) physical and 2) mental.
- Acetaminophen consumption
- WOMAC VAS Stiffness subscore
- WOMAC VAS Physical Function subscore

Summary of efficacy findings

- There is one published clinical trial comparing Gel-One to placebo in 375 patients with osteoarthritis of the knee. The primary endpoint in this trial was the reduction of WOMAC VAS pain scores from baseline.
- The primary endpoint (WOMAC VAS pain score) was analyzed using spline modeling. This statistical technique utilizes all available WOMAC VAS pain score data through week 13. Longitudinal modeling was used to assess the primary endpoint at baseline and for weeks 6 through 13. The longitudinal model was used as the confirmatory model.
- Gel-One® was found to be effective for up to 13 weeks in reducing WOMAC VAS Pain subscores. There was a significant reduction in pain of 6.93 mm on the 100mm WOMAC VAS Pain Scale.
- The initial analysis using random effects in the spline modeling of the primary endpoint did not demonstrate statistical significance. The sponsor excluded the random effect from the statistical model and a statistical difference was found in the primary endpoint favoring Gel-One at 13 weeks. The FDA statistician did concur with the subsequent analysis of the data by the manufacturer showing a statistical difference at 13 weeks.
- Secondary endpoints were analyzed in a sequential manner. If statistical significance was not met for a secondary endpoint, subsequent endpoints were not analyzed. The following efficacy measures did not result in statistical significance between groups: OMERACT-OARSI Response, Total WOMAC VAS Score, WOMAC VAS Stiffness subscore, WOMAC VAS Physical Function subscore.
- No head-to-head trials with other hyaluronate or hylan products are available for comparison.
- There are no data for repeat administration of Gel-One®.

WOMAC VAS Pain subscore reduction at 13 weeks (Intent to Treat Population N = 375)	Two-sided lower 95% Confidence Limit	P-value (two-sided)
6.39 mm	0.37 mm	0.0374

Adverse Events (Safety Data)[1,2,3]

Deaths and Other Serious Adverse Events (Sentinel Events)

No deaths or serious adverse drug reactions resulting in discontinuation of therapy were noted.

Synvisc®, or cross-linked hyaluronic acid, has been shown to cause rare localized inflammatory reactions, pseudosepsis, granulomatous inflammation and severe acute inflammatory reactions (SAIR) after the second or third dose or with subsequent courses of Synvisc®. These adverse reactions have not been observed with Gel-One®. However, there are no data for repeat intra-articular injection with Gel-One®.

Common Adverse Events[5]

	Gel-One®	**Placebo**	**p-value**
Knee joint swelling	14.1%	11.7%	0.63
Knee joint effusion	11.2%	10.2%	0.86
Knee/hip arthralgia	7.6%	9.4%	0.56

Other Adverse Events[1]

	Gel-One®	**Placebo**
Knee joint stiffness	0.8%	0.8%
Knee muscular weakness	0.8%	0.8%
Back pain	0.4%	0.8%
Knee muscle spasms	0.4%	0%
Knee synovitis	0.4%	0%
Injection site pain	2%	0.8%
Effusion	0.4%	0.8%
Injection site erythema	0.4%	0.8%
Injection site bruising	0.4%	0%
Swelling	0.4%	0%
Erythema	0.8%	0%
Rash	0.4%	0%
Pruritic rash	0.4%	0%
Dizziness	0.8%	0%
Tension headache	0.4%	0%
Increased alanine aminotransferase	0.4%	0%
Increased white blood cell count	0.4%	0%
Hypertension	0.4%	0%

Table adapted from the product labeling

Tolerability

For further details on the safety results of the clinical trials, refer to *Appendix: A Clinical* Trials.

Contraindications[1,2,3]

Gel-One® is contraindicated in patients with a known hypersensitivity or allergy to Gel-One® or other sodium hyaluronate preparations.

Gel-One® is contraindicated in patients with skin diseases or infections in the area of the injection site.

Warnings and Precautions[1,2,3]

Use with caution in patients who are allergic to cinnamon or bird products (feathers, eggs, poultry proteins).

Disinfectants containing quaternary ammonium salts should not be used concomitantly, because sodium hyaluronate may form a precipitate in the presence of these disinfectants.

Gel-One® should not be injected intravascularly, extra-articularly, or into the synovial tissue and capsule.

Gel-One® has not been tested to show pain relief in joints other than the knee or for conditions other than OA.

Safety and efficacy of repeat treatments have not been established.

Safety and efficacy in severely inflamed knee joints have not been established.

Special Populations[1,2,3]

Gel-One® has not been tested in patients who are pregnant, mothers who are nursing, or anyone 21 years of age or younger.

Post marketing Safety Experience

No data available.

Sentinel Events

No sentinel events have been reported.

Look-alike / Sound-alike (LA/SA) Error Risk Potential

As part of a JCAHO standard, LA/SA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from four data sources (Lexi-Comp, USP Online LA/SA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LA/SA confusion:

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Gel-One® 1% (10mg/ml)	None	None	None	Gel-Kam Synvisc-One®
Hyaluronate	None	None	None	Hyalgan Other HA products Hyaluronidase

Drug Interactions[1]

Drug-Drug Interactions

There are no known significant drug-drug interactions.

Drug-Lab Interactions

There are no known significant drug-lab interactions.

Acquisition Costs

Refer to VA pricing sources for updated information.

Conclusions

Gel-One® is a cross-linked hyaluronate product approved by the FDA as a biological device for the treatment of OA of the knee in patients who have not responded to non-pharmacological therapy, NSAIDs, or simple analgesics. It is the seventh HA or hylan product to be approved for use in the U.S. It is administered as a single intra-articular injection.

In one clinical study, cross-linked hyaluronate (Gel-One®) was shown to be effective for up to 13 weeks in reducing WOMAC VAS pain scores versus placebo. Other secondary endpoints were not statistically different from placebo. Currently, there are no data for use in joints other than the knee. Safety and efficacy have not been directly compared to other HA or hylan products so differences in safety or efficacy between Gel-One® and other HA or hylan products are unknown. Available data comparing other HA products do not support the use of one HA product over another. Common side effects of Gel-One® are similar to other HA products and include knee joint swelling, effusion, and arthralgia. No serious adverse events were reported and no pseudosepsis has been associated with Gel-One® thus far, but data are lacking for repeat injection.

References:

1. Gel-One® [package insert]. Warsaw, IN: Zimmer; 2011.

2. Gel-One® – P080020. Food and Drug Administration Web site. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cftopic/pma/pma.cfm?num=p080020. Accessed December 20, 2012.

3. Gel-One® Cross-linked Hyaluronate. Zimmer. http://www.zimmer.com/en-US/hcp/common/product/gel-one.jspx?cate=knee. Accessed December 20, 2012.

4. Strand V, Baraf HSB, Lavin PT, Lim S, Hosokawa H. A multicenter, randomized controlled trial comparing a single intra-articular injection of Gel-200, a new cross-linked formulation of hyaluronic acid, to phosphate buffered saline for treatment of osteoarthritis of the knee. *Osteoarthr Cartil.* 20;2012:350-356.

5. Viscosupplementation for Osteoarthritis of the Knee: Intra-Articular Administration of Hyaluronan (Hyaluronic Acid) and Hylan G-F 20 Products. VHA Pharmacy Benefits Management Services and the Medical Advisory Panel. June 2008. Available at: http://www.pbm.va.gov/DrugClassReviews.aspx

6. Synvisc-One® [package insert]. Ridgefield, NJ: Genzyme; 2010.

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Appendix: A Clinical Trials[4]

A literature search was performed on PubMed/Medline using the terms "cross linked hyaluronate", "cross-linked hyaluronate", "gel-200", "gel 200", "gel one", and "gel-one". The search was limited to studies published in the last 5 years, performed on humans, and published in English. Review articles, the product's package insert, and the FDA website were searched for relevant clinical trials. The study included is the only randomized controlled clinical trial published in the manufacturer's New Drug Application to the FDA.

Trial 1

Citation	Strand V, Baraf HSB, Lavin PT, Lim S, Hosokawa H. A multicenter; randomized controlled trial comparing a single intra-articular injection of Gel-200, a new cross-linked formulation of hyaluronic acid, to phosphate buffered saline for treatment of osteoarthritis of the knee. *Osteoarthr. Cartil.* 20;2012:350-356.
Study Goals	To determine the safety and efficacy of a single injection of Gel-200 versus phosphate buffered saline (PBS) for treatment of symptomatic osteoarthritis (OA) of the knee.

Methods	**Study Design:**
	• Double-blind, multi-center, randomized controlled trial
	
	Study Groups:
	• Two-thirds of participants received a single intra-articular injection of Gel-200 (30mg cross-linked hyaluronic acid in 3ml)
	• One-third of participants received a single intra-articular injection of phosphate buffered saline (3ml)
	
	Efficacy/Outcome Measures:
	• Primary outcome:
	  • Patient reported Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscores by 100-mm Visual Analog Scale (VAS) in the affected knee at week 13.
	• Secondary outcome:
	  • Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International (OMERACT-OARSI) "strict" responses defined by:
	  • Improvements from baseline in WOMAC pain or physical function subscores ≥50% with absolute changes ≥20mm
	  • ≥20% improvements with absolute change ≥10mm in WOMAC pain or physical function subscores and/or patient global assessments of disease activity
	Data Analysis
	• Analysis of effectiveness was performed, intent-to-treat, defined as all randomized patients who received at least one post-injection visit.
	
	Criteria
	• Inclusion criteria:
	  • 40-80 years of age
	  • Diagnosis of knee osteoarthritis
	  • Pain in the affected knee for ≥4 weeks in duration while standing or walking
	  • Kellgren-Lawrence (K-L) grade 1-3 by x-ray
	  • WOMAC pain subscores ≥40mm in affected knee and

<table>
<tr><td></td><td>≤20mm in contralateral knee by 100mm VAS
• Willing to discontinue current osteoarthritis treatments other than allowed medications (NSAIDS, nonprescription herbal therapies, and chondroprotective agents (e.g. oral HA, glucosamide chondroitin sulfate, minocycline))
• Stable for ≥4 weeks prior to entry
• Exclusion criteria:
• K-L grade 4 of the treated knee
• Inflammatory diseases of the knee other than osteoarthritis
• Severe knee joint effusion
• Severe malalignment of the knee
• History of joint replacement of the knee or hip within the previous 12 months
• Arthroscopy of either knee within 3 months
• Intra-articular injections with corticosteroids within the past 4 weeks
• Intra-articular hyaluronic acid injections within the past 6 months
• Serious systemic diseases
• Infectious/inflammatory skin diseases in the area of the affected knee</td></tr>
<tr><td>Results</td><td>Enrollment:
• 375 patients met eligibility criteria, were randomized to treatment, and comprised the pre-defined intent-to-treat population
• 247 patients received Gel-200
• 128 patients received phosphate buffered saline
• Trial was conducted August 2006-December 2007

Baseline Characteristics:
• No statistically significant differences were identified between treatment groups

<table>
<tr><th>Baseline Characteristics</th><th>Gel-200 (247)</th><th>Phosphate Buffered Saline (128)</th></tr>
<tr><td>Gender
Male
Female</td><td>
100 (40.5%)
147 (59.5%)</td><td>
51 (39.8%)
77 (60.2%)</td></tr>
<tr><td>Age, years (mean ± SD)</td><td>60.9±10.24</td><td>60.3±9.97</td></tr>
<tr><td>BMI, kg/m^2 (mean±SD)</td><td>28.3±4.14</td><td>28.7±3.83</td></tr>
<tr><td>Study knee
Right
Left</td><td>
136 (55.1%)
111 (44.9%)</td><td>
62 (48.4%)
66 (51.6%)</td></tr>
<tr><td>K-L x-ray scores
Grade 1
Grade 2
Grade 3</td><td>
21 (8.5%)
94 (38.1%)
132 (53.4%)</td><td>
18 (14.1%)
47 (36.7%)
63 (49.2%)</td></tr>
<tr><td>Duration of OA in study knee, months (mean±SD)</td><td>42.0±51.4</td><td>31.2±41.2</td></tr>
<tr><td>WOMAC pain subscore</td><td>70.7±14.42</td><td>68.0±13.05</td></tr>
<tr><td>Total WOMAC score</td><td>69.5±15.99</td><td>67.8±14.68</td></tr>
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	<table><tr><td>WOMAC physical function subscore</td><td>68.9±17.41</td><td>67.6±15.80</td></tr><tr><td>WOMAC stiffness subscore</td><td>71.6±17.48</td><td>69.3±17.31</td></tr></table> **Clinical Outcomes:** <table><tr><th>Measurements at Week 13</th><th>Estimated Difference (95% CI)</th><th>P-Value</th></tr><tr><td>WOMAC pain subscores</td><td>6.39 (0.37, 12.41)</td><td>0.037</td></tr><tr><td>Total WOMAC score</td><td>5.64 (-0.20, 11.47)</td><td>0.058</td></tr><tr><td>WOMAC physical function subscores</td><td>5.42 (-0.47, 11.31)</td><td>0.071</td></tr><tr><td>WOMAC stiffness subscores</td><td>4.91 (-1.31, 11.14)</td><td>0.122</td></tr><tr><td>Physician global assessment</td><td>3.56 (-1.48, 8.60)</td><td>0.166</td></tr><tr><td>Patient global assessment</td><td>0.92 (-4.63, 6.47)</td><td>0.746</td></tr></table> **Adverse Reaction:** • The incidence of adverse reactions was similar in both treatment groups. • 182 treatment-related adverse events were reported in 100 patients, 67 patients receiving Gel-200 (26.9%) and 33 patients receiving phosphate buffered saline (25.8%) • The most common treatment-related adverse reactions included joint swelling, effusions, and arthralgia, without significant differences between treatment groups. • Serious adverse events were reported by eight patients, including five cases of cancer. However, none were judged by investigators to be related to study treatment, although all serious adverse events occurred in the Gel-200 group.
Conclusion	• Treatment with a single injection of Gel-200 offers statistically significant and clinically meaningful improvements in pain and physical function in patients with knee osteoarthritis over 13 weeks.
Critique	**Strengths:** • Primary endpoint result was statistically significant • No allergic reactions, pseudosepsis, or serious adverse events were noted, supporting a favorable safety profile for this product. However, these events occurred with the second or third injection or with subsequent treatment courses of Synvisc and since there are no data for repeat injection with Gel-One, it is unknown if similar events may occur with this agent. **Limitations:** • There was no statistically significant difference between Gel-200 and phosphate buffered saline in patient global assessment of disease activity or other secondary endpoints. • Small sample size • Trial completed in 2007, delay in publishing and product approval?